# The effects of sildenafil citrate on human sperm function in healthy volunteers

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*Aims* This double-blind, randomized, four-period, two-way crossover study was conducted to evaluate the acute effects of oral sildenafil (100-mg single dose) on sperm motility, count, density, morphology and vitality as well as ejaculate volume and viscosity in healthy male subjects. The concentrations of sildenafil and its primary circulating metabolite UK-103,320 were measured in ejaculate and compared with those in plasma. The study also included assessments of safety and tolerability.

*Methods* A total of 17 healthy male volunteers aged 19–34 years were randomized to receive a single 100-mg dose of sildenafil for two periods and a single dose of placebo for two periods, with each period separated by a minimum of 5–7 days. Sperm and ejaculate properties were evaluated from semen samples taken at screening and 1.5 h after dose. An additional semen sample was collected 4 h after dose, and drug and metabolite concentrations were measured in this sample and the sample taken 1.5 h after dose for comparison with plasma concentrations. Blood samples were collected before each dose and 0.25, 0.5, 1, 2, 3, 4 and 6 h after dose for measurement of sildenafil and metabolite concentrations.

*Results* Sildenafil had no statistically significant effect on sperm motility, count or density; the percentage of abnormal sperm forms; or the percentage of living sperm. It also did not affect ejaculate volume or viscosity. All measures were within normal ranges. Sildenafil distributed into the semen rapidly, resulting in significant correlations between concentrations of sildenafil in the semen and total ($R^2 = 0.588$) or free ($R^2 = 0.454$) plasma concentrations ($P < 0.0001$). Total semen concentrations of sildenafil were 18% of total plasma concentrations. UK-103,320 appeared to distribute more slowly from the plasma into the semen, resulting in a lack of correlation between semen and plasma concentrations. The amount of sildenafil and UK-103,320 in the ejaculate was small ($< 2 \times 10^{-4}$% of the administered dose at 1.5 h). Sildenafil was well tolerated; no patient withdrew from the study due to adverse events attributed to sildenafil.

*Conclusions* These results indicate that a single 100-mg oral dose of sildenafil does not have an adverse effect on sperm function or ejaculate quality.

*Keywords:* sildenafil, UK-103,320, sperm, ejaculate, safety, pharmacokinetics, protein binding

## Introduction

Erectile dysfunction (ED) is a widespread condition that can have a negative impact on quality of life [1], affecting both older and younger men [2]. Until recently, no effective oral therapy existed. Available treatments were

highly cumbersome or invasive, and many patients and their partners found them unacceptable solutions to the problem [3].

Sildenafil citrate (Viagra[®], Pfizer) is the first oral agent to be introduced for the management of ED. When administered before sexual activity, it produces reliable efficacy, good tolerability and rapid absorption that yields prompt onset of action; it has a plasma half-life that produces an appropriate duration of action while avoiding accumulation on repeated once-daily use [4]. In clinical

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trials, sildenafil has been shown to increase the duration and rigidity of penile erection in response to visual sexual stimuli in a hospital setting [4] and to greatly enhance the ability to achieve erections, leading to successful completion of intercourse in the home setting [5].

A large number of drugs can be transported into the seminal fluid, where they can have direct effects on sperm function, physiology, metabolism or genetic composition [6]. Several drugs have been shown to affect sperm motility in particular [7]; these include compounds with phosphodiesterase (PDE)-inhibitory activity that have the potential to increase motility [8, 9]. One such drug, pentoxifylline, which is a cyclic adenosine monophosphate (cAMP) PDE inhibitor, has been shown to stimulate human sperm motility both *in vitro* and *in vivo* [10].

Sildenafil is a potent and selective inhibitor of the cyclic guanosine monophosphate (cGMP)-specific PDE type 5 enzyme [11] and thus enhances the activity of the nitric oxide–cGMP pathway that promotes penile erection. The drug is relatively lipophilic (log $D_{7.4} = 2.7$) and would therefore be expected to distribute into the seminal fluid. It is likely that sildenafil will be used by men with ED as an aid to procreation, especially by younger patients who have ED secondary to spinal cord injury. Because of this, a clinical study was conducted to investigate the effect of a single oral dose of sildenafil on a number of semen and sperm motility and morphology parameters. In addition, the concentrations of sildenafil and its major circulating metabolite (UK-103,320) were measured in semen samples and compared with those obtained in plasma.

## Methods

### Subjects and study design

Healthy male volunteers were eligible for entry into this study if they were between the ages of 18 and 45 years, weighed between 60 and 100 kg, and had a body mass index of 18–25 kg m$^{-2}$. Exclusion criteria were as follows: azoospermia or extreme oligospermia, asthenospermia, or teratospermia or any combination of these at baseline; clinically significant disease; allergy; abnormality in prestudy laboratory data and physical examination; use of any medication except paracetamol in the 3 weeks before the study; use of any experimental drug in the 4 months before the study; alcohol consumption of more than 28 units per week; drug abuse; and use of more than 10 cigarettes (or equivalent tobacco) per day. Written informed consent was obtained from each subject before study entry, and the study protocol was reviewed and approved by the Regional Committee for Medical Research Ethics, Oslo, Norway.

This double-blind, randomized, four-period, two-way crossover study compared 100-mg doses of sildenafil with placebo, each administered as single oral doses for two periods separated by a washout period of at least 5–7 days. The repeat administration of both sildenafil and placebo was performed to correct for the inherent intrasubject variability in sperm motility and morphology measures.

Subjects who met the inclusion criteria underwent a prestudy screening in the 3 weeks before the start of the study that consisted of a physical examination, measurement of supine blood pressure and pulse rate, a 12-lead electrocardiogram, laboratory safety tests (blood and urine) and a urine screen for drugs of abuse. A semen sample was also collected to exclude subjects who were azoospermic or had sperm motility that was not assessable.

The subjects were asked not to ejaculate for a minimum of 3 days before each dose of study drug. They were not permitted to consume products containing caffeine, methylxanthines or alcohol and were asked to refrain from unaccustomed exercise in the 48 h before each dose of study drug and while at the study centre. The subjects also were required not to use prescription or over-the-counter drugs during the study and were not permitted to smoke at the study centre.

The sponsor of the study provided sildenafil as 100-mg tablets and matching placebo tablets, and the order of dosing was randomized. The subjects were asked to have breakfast before attending the study centre on each of the four mornings of dosing. They did not receive study drug until a minimum of 2 h had elapsed after their last meal. All study medications were taken under supervision in the study centre, with 240 ml of water, while standing or seated upright. Lunch and dinner were provided at 2 and 6 h after dose (after blood sampling). Noncaffeinated drinks were permitted from 4 h after dose.

### Assessments

*Sperm and semen parameters* Semen samples were obtained at screening and 1.5 and 4 h after dose. Only the screening and 1.5-h samples were analysed for sperm motility. For evaluation of sperm motility, aliquots of ejaculate were transferred to a Hamilton Thorn motility analyser after a liquefaction period of 30 min at room temperature as described in previous publications from our clinic [12, 13]. The following parameters were determined:

Percentage of sperm exhibiting all forms of movement (% motile)

Percentage of static sperm (% static)

Percentage of motile sperm that swam rapidly (% rapid)

Percentage of motile sperm that swam progressively (% progressive)

Average velocity ($\mu$m s$^{-1}$) of motile sperm swimming progressively (progressive motility)

Mean lateral head displacement ($\mu$m).

Data regarding the reproducibility of repeated motility measurements (five times) on the same 10 ejaculates have been computed. The average coefficients of variation for percentage motile, percentage rapid, percentage progressive, progressive motility and mean lateral head displacement were 8.2%, 6.3%, 7.2%, 3.1% and 7.4%, respectively. The sperm samples used in this validation study were classified as borderline to normal. Normal values for motility are the same as those recommended by the manufacturer of the motility analyser, which corresponds to our own clinical experience.

In addition, the samples were analysed for sperm count using a Bürker chamber after diluting and immobilizing the sperm with 5% chloramine T (1:10). An assessment of morphology and vitality was made after staining with eosin Y and Harris haemotoxylin. Ejaculate volume was measured gravimetrically and viscosity was assessed in terms of the number of seconds for drop formation to occur from a standard 50-$\mu$l capillary tube. These analyses were carried out in a fertility clinic with access to 2000 patients per year. The definitions of normality were derived from data obtained from these patients and described in a number of previous publications [14–17].

*Sildenafil plasma and semen concentrations*   Blood samples (7 ml) were collected at time 0 (predose) and after each dose of study drug at 0.25, 0.5, 1, 2, 3, 4 and 6 h after dose for assays of total concentrations of sildenafil and UK-103,320. Additional blood samples were taken 1 and 4 h after dose to assess plasma protein binding of sildenafil and UK-103,320 using equilibrium dialysis. Samples were collected in heparinized tubes and centrifuged for 10 min at room temperature and 1500 *g*, and the plasma was separated and stored at −20°C before assay.

Semen samples were collected at 1.5 and 4 h after dose for assay of sildenafil and UK-103,320. Samples were frozen until assay (after pharmacodynamic analysis for the sample obtained 1.5 h after dose). For both semen and plasma, assays for the drug and its metabolite were conducted using automated sequential trace enrichment of dialysates and previously validated high-pressure liquid chromatography with ultraviolet detection [18]. The limits of quantification were 1 ng ml$^{-1}$ for both sildenafil and UK-103,320. During analysis for the estimation of total plasma concentrations and dialysate and donor analyte concentrations for determination of protein binding, the overall imprecision for both sildenafil and UK-103,320 did not exceed 6% across the concentration range of 3–200 ng ml$^{-1}$. The inaccuracy (% bias) for these assays ranged from −5% to 3% across the same concentration

range. During the analysis for the estimation of total semen analyte concentrations, insufficient data were obtained to determine the overall imprecision of the assay. However, the inaccuracy (% bias) was from −4.8% to −1% for sildenafil and from −0.5% to 0.8% for UK-103,320 across the concentration range of 3–200 ng ml$^{-1}$.

## Pharmacokinetic analysis

All pharmacokinetic parameters were calculated by noncompartmental analysis using WinNonlin™ Version 1.1 (Pharsight Corporation). The following pharmacokinetic parameters were derived for sildenafil and UK-103,320 from the individual concentration–time curves: the maximum observed plasma concentration, the time to achieve maximum observed plasma concentration, the area under the plasma concentration–time curve from zero time to the last measured concentration using a linear trapezoidal method, plasma protein binding calculated as (dialysate concentration/donor plasma analyte concentration) × 100 and amount of drug in the semen 1.5 h after dose, calculated as semen concentration × semen volume.

## Safety and tolerability

Observed or volunteered adverse events were recorded throughout the study. A physical examination and supine blood pressure and pulse rate measurements were performed on each morning of dosing and after blood sampling 6 h after dose. Laboratory safety tests were conducted before administration of the first dose of study drug, and urine screens for drugs of abuse and alcohol breath tests were performed on each morning of dosing. A follow-up visit was conducted 7–10 days after the last dose of study drug.

## Statistical evaluation

Sperm motility parameters were subject to analysis of variance that ascribed variation in the data to subjects, periods, treatments, subject-by-period interaction and analysis time. Adjusted treatment means, differences and 95% confidence intervals were obtained for each treatment averaging over analysis time and for each analysis time averaging over treatments. Sperm and ejaculate parameters were analysed in a similar manner but excluding terms involving analysis time. Ejaculate viscosity data were log-transformed to satisfy the distributional assumptions of the analysis of variance and presented as (back-transformed) geometric means. The relationships between total amounts and concentrations of sildenafil and UK-103,320 in the semen and the corresponding total and free drug plasma concentrations were analysed using

linear regression methods. Individual values were averaged over replicate treatments. All statistical analyses were performed using SAS version 6.0 (SAS Institute Inc.).

## Results

### Demographic characteristics

Seventeen healthy male volunteers were enrolled in the study and eligible for safety assessment. One subject was withdrawn from the trial because of a serious adverse event after receiving placebo (considered unrelated to treatment). The remaining 16 subjects completed the study. The subjects were between 19 and 34 years of age (mean 24 years) and weighed between 64 and 98 kg (mean 80 kg). All subjects were white. No significant medical conditions relevant to the study were noted before entry.

### Sperm and semen parameters

The mean values for the sperm motility parameters were all within the normal ranges predefined by the study centre. No significant difference was observed between sildenafil and placebo for any parameter (Table 1), indicating no effect on sperm function. For percentage motile, percentage static, percentage rapid and percentage progressive, the analysis of variance showed no significant time effect (i.e. no difference between parameters measured 0.5 and 2 h after collection). However, there was some evidence of a small effect of time on progressive motility; the adjusted means, averaged over both treatment groups, were 26.8 μm/s at 0.5 h after collection and 28.8 μm/s at 2 h after collection ($P < 0.0001$), indicating that progressive motility is slightly faster 2 h after collection than 30 min after collection. A time effect was also noted for lateral head displacement, which increased significantly from 2.28 μm at 0.5 h to 2.47 μm at 2 h after collection. These differences were independent of treatment and of no clinical significance.

Similarly, sildenafil was equivalent to placebo in its effects on all secondary semen analysis parameters, including sperm count, density, morphology (% abnormal forms) and vitality (% living sperm) as well as ejaculate volume and viscosity (Table 2). These variables were also all within the normal ranges predefined by the study centre.

### Pharmacokinetics

Mean values for the pharmacokinetic parameters of sildenafil and UK-103,320 are presented in Table 3, and the mean values for plasma and semen concentrations and total amount of drug in semen are summarized in Table 4. Sildenafil was rapidly absorbed with a mean time to achieve the maximum observed plasma concentration of 1.4 h after dose. The maximum observed plasma concentration of the metabolite also occurred at 1.4 h after dose, indicating rapid formation of the metabolite from the parent drug (Figure 1). Plasma concentrations of UK-103,320 were approximately 40% those of the parent drug. Protein binding was similar for both drug and metabolite (93–95%) at 1 and 4 h after dose.

The concentrations of sildenafil in the semen at 1.5 and 4 h after dosing were 51.4 and 15.5 ng ml$^{-1}$, respectively. The concentrations of UK-103,320 in the semen at 1.5 and 4 h after dosing were 5.12 and 7.10 ng ml$^{-1}$, respectively (Table 4). Concentrations of sildenafil in semen were greater than the free plasma concentrations of sildenafil, although the total amount of sildenafil (188 ng) and UK-103,320 (17.7 ng) in the ejaculate was small (each $< 0.0002\%$ of the administered dose at 1.5 h after dose). Mean concentrations of sildenafil in semen were 3.3-fold higher at 1.5 h after dose than at 4 h after dose, which is consistent with the ratio of mean plasma concentrations at these time points. Mean semen concentrations were approximately 18% of mean plasma concentrations at the same time points.

**Table 1** Effect of sildenafil on sperm motility parameters. All data reported as adjusted means.

| Parameter | Normal values | Sildenafil | Placebo★ | Sildenafil–placebo (95% confidence intervals) |
|---|---|---|---|---|
| Motile (%) | >50 | 60.1 | 60.2 | −0.1 (−5.2, 5.0) |
| Static (%) | <50 | 39.9 | 39.8 | 0.1 (−5.0, 5.2) |
| Rapid (%) | >25 | 37.2 | 39.7 | −2.5 (−6.4, 1.3) |
| Progressive (%) | >15 | 25.9 | 27.4 | −1.5 (−4.5, 1.5) |
| Progressive motility (μm s$^{-1}$) | >25 | 27.5 | 28.2 | −0.7 (−1.61, 0.20) |
| Mean lateral head displacement (μm) | | 2.36 | 2.40 | −0.04 (−0.16, 0.08) |

★$P =$ Not significant for all comparisons *vs* sildenafil.

**Table 2** Effect of sildenafil on secondary semen analysis parameters. For ejaculate viscosity, data are presented as adjusted geometric means.

| Parameter | Normal values | Sildenafil | Placebo* | Sildenafil–placebo (95% confidence intervals) |
|---|---|---|---|---|
| Sperm count ($\times 10^6$) | 100–500 | 389.7 | 367.4 | 22.3 (−44.7, 88.7) |
| Sperm density ($\times 10^6$ ml$^{-1}$) | 50–150 | 117.9 | 107.4 | 10.5 (−8.5, 29.4) |
| Abnormal forms (%) | <85 | 82.03 | 80.88 | 1.16 (−0.01, 2.32) |
| Living sperm (%) | >80 | 83.22 | 84.94 | −1.7 (−5.3, 1.8) |
| Ejaculate volume (ml) | 2.5–6 | 3.663 | 3.636 | 0.027 (−0.299, 0.352) |
| Ejaculate viscosity (s) | <10 | 3.803 | 4.285 | 88.7% (72.4, 108.8)† |

*$P=$ Not significant for all comparisons *vs* sildenafil; †ratio between geometric means.

**Table 3** Mean pharmacokinetic parameters for sildenafil and UK-103,320. Geometric means reported for $AUC_6$ and $C_{max}$, arithmetic means reported for $t_{max}$ and plasma protein binding.
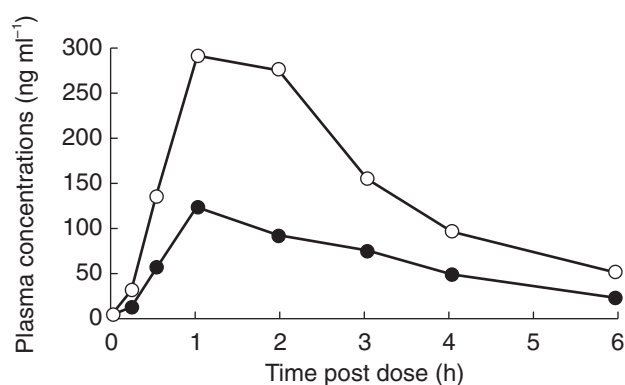
| Parameter | Sildenafil $\pm$ s.d. | UK-103,320 $\pm$ s.d. |
|---|---|---|
| $AUC_6$ (ng ml$^{-1}$ h) | 841 $\pm$ 293 | 341 $\pm$ 157 |
| $C_{max}$ (ng ml$^{-1}$) | 331 $\pm$ 115 | 125 $\pm$ 59 |
| $t_{max}$ (h) | 1.40 $\pm$ 0.49 | 1.44 $\pm$ 0.65 |
| Plasma protein binding (% free) | | |
| 1 h after dose | 5.71 $\pm$ 2.25 | 6.87 $\pm$ 2.65 |
| 4 h after dose | 4.71 $\pm$ 1.64 | 5.50 $\pm$ 1.65 |

$C_{max}=$ Maximum observed plasma concentration; $t_{max}=$ time to achieve maximum observed plasma concentration; $AUC_6=$ area under the plasma concentration–time curve from zero time to the last measured concentration.



**Figure 1** Mean plasma concentrations of sildenafil (○) and UK-103,320 (●) over time from 17 healthy male volunteers ($n=17$) administered a 100-mg oral dose of sildenafil.

**Table 4** Total and free plasma concentrations, semen concentrations and total amount of drug in semen for sildenafil and UK-103,320.

| Parameter | Sildenafil $\pm$ s.d. | UK-103,320 $\pm$ s.d. |
|---|---|---|
| Total plasma concentration (ng ml$^{-1}$) | | |
| 1–2 h | 286 $\pm$ 117 | 106 $\pm$ 50 |
| 4 h | 91 $\pm$ 36 | 47 $\pm$ 21 |
| Free plasma concentration (ng ml$^{-1}$) | | |
| 1–2 h | 14.9 $\pm$ 4.9 | 7.0 $\pm$ 3.0 |
| 4 h | 4.2 $\pm$ 2.3 | 2.5 $\pm$ 1.2 |
| Total semen concentration (ng ml$^{-1}$) | | |
| 1.5 h | 51.4 $\pm$ 30.1 | 5.12 $\pm$ 3.57 |
| 4 h | 15.5 $\pm$ 5.6 | 7.10 $\pm$ 4.50 |
| Total amount of drug in semen (ng) | | |
| 1.5 h | 188 $\pm$ 14.6 | 17.7 $\pm$ 14.7 |

Arithmetic means reported for all parameters.

Mean UK-103,320 semen concentrations were 1.4-fold higher at 4 h after dose than at 1.5 h after dose, which was inconsistent with the ratio of mean plasma concentrations at the same time points (2.2-fold higher at 1.5 h than at 4 h). Mean semen concentrations of the metabolite were approximately 5% and 15% of the mean plasma concentrations at 1.5 h and 4 h, respectively.

Analyses of the individual subject data showed that the relationships between concentrations of sildenafil in the semen and total ($R^2=0.588$) or free ($R^2=0.454$) plasma concentrations were highly significant ($P<0.0001$; Figure 2). There was no evidence of a significant relationship between UK-103,320 semen concentrations and either total or free plasma UK-103,320 concentrations.

*Safety and tolerability*

Adverse events considered by the investigator to be related to treatment occurred in 11 of 16 subjects (69%) following administration of sildenafil and in three of 17 subjects (18%) following administration of placebo (Table 5). The
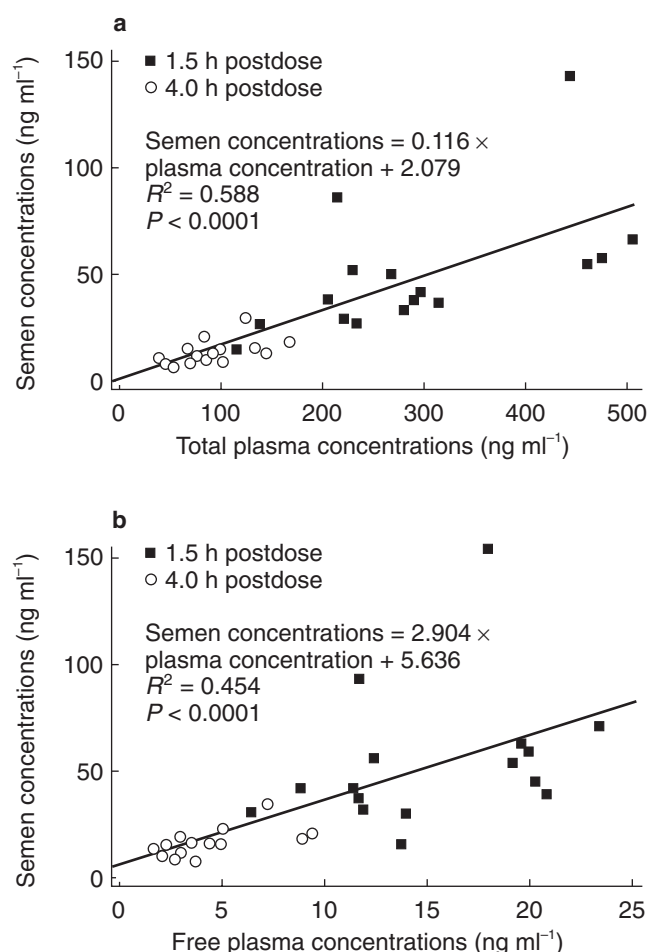
**a**



**b**



**Figure 2** Correlation of sildenafil concentrations in semen to total plasma concentrations (a) and free plasma concentrations (b).

**Table 5** Incidence of adverse events following treatment with sildenafil or placebo.

|  | *Sildenafil* | *Placebo* |
|---|---|---|
| All cause treatment-emergent adverse events (withdrawals) | 14/16 (0) | 7/17 (1)⋆ |
| Treatment-related adverse events | 11/16 | 3/17 |
| Flushing | 6 | 1 |
| Headache | 5 | 1 |
| Dizziness | 3 | 1 |
| Abnormal vision† | 3 | 0 |

⋆This subject discontinued because of severe back pain related to a slipped disc; †each case was a mild and transient disturbance in colour discrimination.

most frequently reported adverse events were flushing, headache, dizziness and abnormal vision and were generally mild to moderate in severity. No subject discontinued treatment due to adverse effects related to sildenafil. No clinically significant changes in laboratory values were reported.

## Discussion

A total of 17 healthy male volunteers were enrolled in this double-blind, placebo-controlled study to determine the pharmacokinetics of sildenafil and its pharmacodynamic effects on sperm function and ejaculate quality. Sixteen subjects completed the study. Although sildenafil is a member of a drug class (PDE inhibitors) previously shown to have some effects on sperm motility [8, 9], a comparison of sildenafil *vs* placebo on a wide variety of measures in this study showed no effect on sperm motility, count, density, morphology or vitality and no alteration in ejaculate volume or viscosity. The small but statistically significant increase in progressive motility and lateral head movement observed between the parameters measured 0.5 h and 2 h after collection after both sildenafil and placebo dosing is most likely due to one or a combination of several factors. These factors could include a reduction in viscosity of the seminal plasma due to the action of proteases, an uptake of energy substrates such as fructose from the semen, or alterations in electrolyte levels such as a reduction in $K^+$, which is inhibitory, or an uptake of $Ca^{2+}$, which is stimulatory.

It has been hypothesized that the positive effect of pentoxifylline, a cAMP-specific PDE inhibitor, on sperm motility may be due to its pharmacological action on cAMP metabolism [10]. However, sildenafil is a specific inhibitor of the cGMP-specific type 5 PDE and has no effect on the cAMP-specific PDEs [11]; this may explain the difference between the results obtained here and those obtained with pentoxifylline and other nonspecific PDE inhibitors.

The semen and plasma concentrations of sildenafil suggest that the drug rapidly equilibrates between the blood and the accessory genital glands that produce the constituents of the ejaculate. Total semen concentrations of sildenafil correlated well with total and free plasma concentrations. The concentration of the drug in semen appeared to be greater than its free plasma concentration, indicating a disequilibrium. This may be caused by ion trapping of sildenafil, which is a weak organic base, in the weakly acidic prostatic secretions (pH 6.5). However, previous studies have demonstrated that ion trapping can result in seminal fluid to plasma concentration ratios of 5–10 [19], which emphasizes that several factors are involved in determining the distribution of drugs into the seminal fluid. These factors include the dissociation constant, lipid solubility, equilibration time and plasma protein binding. The amount of sildenafil recovered in the ejaculate was extremely small ($< 2 \times 10^{-4}\%$ of the administered dose 1.5 h after dose). Distribution of the *N*-desmethyl metabolite UK-103,320 into the semen appeared to lag behind that of the parent drug, even

though the times to achieve maximum observed plasma concentration values were concurrent. This may be explained by the fact that the metabolite is more polar than the parent drug and as such distributes less readily into the semen.

Sildenafil was well tolerated, producing no serious adverse events or clinically important changes in vital signs. The most frequently reported adverse events (flushing, headache, dizziness and abnormal vision) were generally consistent with those reported in other studies [4, 5, 20].

This study confirms earlier findings showing the minimal effect of sildenafil on sperm motility and count in men of reproductive age [21, 22]. In a study of 20 healthy male volunteers, Aversa *et al.* found no difference in sperm number, progressive motility or morphologic abnormalities between semen samples obtained 1 h after taking a 100-mg dose of sildenafil or double-blind placebo [23]. An *in vitro* study found no effects on sperm motility at concentrations approximately 4000 times peak semen concentration following the highest recommended therapeutic dose (100 mg) of sildenafil [24]. A negative effect on sperm motility was observed only at extremely high concentrations that were not clinically relevant (40 000 times greater than after a 100-mg oral dose) combined with low pH. Finally, 10 men seeking treatment for infertility had their ejaculatory dysfunction reversed by using sildenafil [25]. Three partners of the 10 men subsequently conceived. These recent findings combined with the results presented in this report suggest that oral sildenafil does not acutely interfere with male fertility.

Although the incidence of ED increases with age, younger men are also affected [2]. As such, it is very likely that a significant number of patients will use sildenafil as an aid to procreation. The results of this study clearly indicate that single oral doses of sildenafil (100 mg) can be safely administered without concern on the part of the physician or the patient regarding adverse effects on sperm or ejaculate quality. The amount of sildenafil and its metabolite in the ejaculate are very low, and concentrations of sildenafil in semen can be accurately predicted based on plasma concentrations.

## References

1 NIH Consensus Development Panel on Impotence. Impotence. *JAMA* 1993; **270**: 83–90.

2 Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol* 1994; **151**: 54–61.

3 Levine SB, Althof SE, Turner LA, *et al.* Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol* 1989; **141**: 54–57.

4 Boolell M, Allen MJ, Ballard SA, *et al.* Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996; **8**: 47–52.

5 Goldstein I, Lue TF, Padma-Nathan H, *et al.* Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998; **338**: 1397–1404.

6 Pichini S, Zuccaro P, Pacifici R. Drugs in semen. *Clin Pharmacokinet* 1994; **26**: 356–373.

7 Gagnon C, ed. *Controls of Sperm Motility: Biological and Clinical Aspects*. Boca Raton. CRC Press, 1990.

8 Schoenfeld C, Amelar RD, Dublin L. Stimulation of ejaculated human spermatozoa by caffeine. *Fertil Steril* 1975; **26**: 158–161.

9 Turner EA, de Aparicio NJ, Turner D, Schwarzstein L. Effect of two phosphodiesterase inhibitors, cyclic adenosine 3′:5′-monophosphate, and a beta-blocking agent on human sperm motility. *Fertil Steril* 1978; **29**: 328–331.

10 Shen MR, Chiang PH, Yang RC, Hong CY, Chen SS. Pentoxifylline stimulates human sperm motility both *in vitro* and after oral therapy. *Br J Clin Pharmacol* 1991; **31**: 711–714.

11 Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue *in vitro* and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 1998; **159**: 2164–2171.

12 Engh E, Clausen OPF, Purvis K, Stien R. Sperm quality assessed by F\flow cytometry and accessory sex gland function in spinal cord injured men after repeated vibration-induced ejaculation. *Paraplegia* 1993; **31**: 3–12.

13 Evenson DP, Jost LK, Marshall D, *et al.* Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic. *Hum Reprod* 1999; **14**: 1039–1049.

14 Purvis K, Tollefsrud A, Rui H. Stability of sperm characteristics in men with disturbances in sperm quality. *Int J Androl* 1989; **12**: 171–178.

15 Engh E, Clausen OPF, Purvis K. Acrosomal integrity assessed by flow cytometry in men with variable sperm quality. *Hum Reprod* 1991; **6**: 1129–1134.

16 Christiansen E, Tollefsrud A, Purvis K. Sperm quality in men with chronic abacterial prostatovesiculitis verified by rectal ultrasonography. *Urology* 1991; **38**: 545–549.

17 Engh E, Clausen OPF, Scholberg A, Tollefsrud A, Purvis K. Relationship between sperm quality and chromatin condensation measured by sperm DNA fluorescence using flow cytometry. *Int J Androl* 1992; **15**: 407–415.

18 Cooper JDH, Muirhead DC, Taylor JE, Baker PR. Development of an assay for the simultaneous determination of sildenafil (Viagra®) and its metabolite (UK-103,320) using automated sequential trace enrichment of dialysates and high-performance liquid chromatography. *J Chromatogr B* 1997; **701**: 87–95.

19 Berger SA, Yavetz H, Paz G, Gorea A, Homonnai Z. Concentration of ofloxacin and ciprofloxacin in human semen following a single oral dose. *J Urol* 1990; **144**: 683–684.

20 Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH. Clinical safety of oral sildenafil citrate (Viagra™) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; **10**: 69–74.

21 Zavos PM, Zarmakoupis-Zavos PN. The use of sildenafil citrate for treatment of male infertility in males with erectile dysfunction. *Obstet Gynecol* 2000; **95**: S49–S50.

22 Burger M, Sikka SC, Bivalacqua TJ, Lamb DJ, Hellstrom WJG. The effect of sildenafil on human sperm motion and function from normal and infertile men. *Int J Impot Res* 2000; **12**: 229–234.

23 Aversa A, Mazzilli F, Rossi T, Delfino M, Isidori A, Fabbri A. Effects of sildenafil (Viagra®) administration on seminal parameters and post-ejaculatory refractory time in normal males. *Hum Reprod* 2000; **15**: 131–134.

24 Andrade JR, Traboulsi A, Hussain A, Dubin N. *In vitro* effects of sildenafil and phentolamine, drugs used for erectile dysfunction, on human sperm motility. *Am J Obstet Gynecol* 2000; **182**: 1093–1095.

25 Kaplan B, Ben-Rafael Z, Peled Y, Bar-Hava I, Bar J, Orvieto R. Oral sildenafil may reverse secondary ejaculatory dysfunction during infertility treatment. *Fertil Steril* 1999; **72**: 1144–1145.